

## **STATISTICAL ANALYSIS PLAN (SAP)**

### **Phase 3 Randomized Controlled Trial Evaluating the Effect of Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) on Hypertension Medication Reduction, Blood Pressure Levels and Others Cardiovascular Risk Factors.**

GATEWAY (GAstric bypass surgery to TrEat patients With steAdy hYpertension)

**Version: 2.0**

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**Coordinating Center:** Research Institute HCor  
Rua Abílio Soares, 250 – Paraíso  
Zip code: 04005-000 São Paulo, SP – Brazil  
Tel: +55 11 3053 -6611 Extension: 8210  
Fax: +55 (11) 3886-4695

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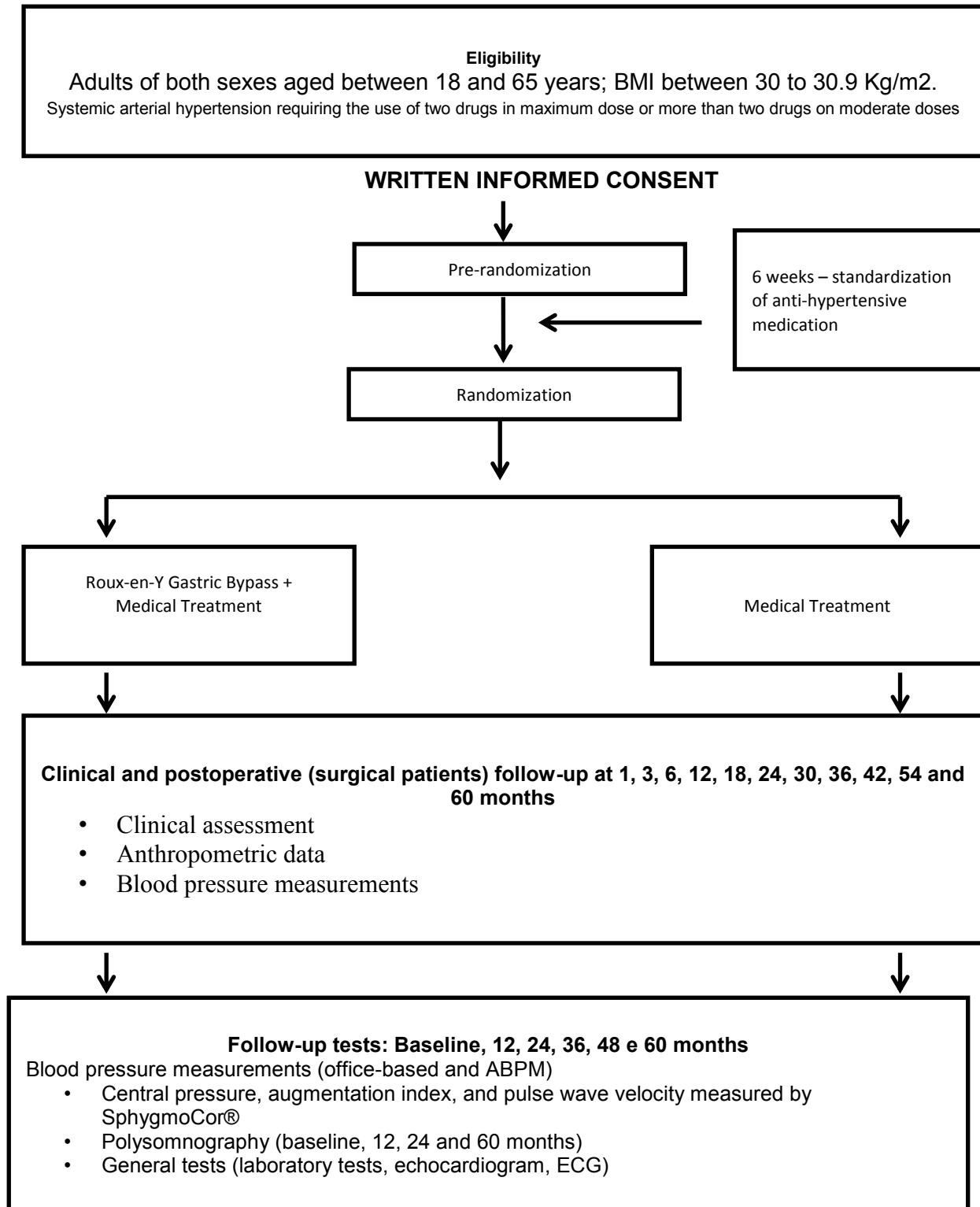
## 1. STUDY OVERVIEW

GATEWAY study is a randomized single-center, non-blinded trial, including patients with obesity grade 1 or 2 (body mass index between 30.0 and 39.9Kg/m<sup>2</sup>) and hypertension using at least two drugs at maximum doses or more than two on moderate doses. Patients were randomized to Roux-en-Y gastric bypass plus medical therapy or medical therapy alone in a 1:1 ratio performed in blocks of 10 patients. The reader of this Statistical Analysis Plan (SAP) is also encouraged to read the clinical trial protocol which provides the detail on the conduct of the study, definitions of standard medical therapy and the interventional procedure, the operational aspects of clinical assessments, and the timings of individual patient assessments.

This SAP contains the description of the sample size determination process, definitions of analysis populations, end points, and details on the statistical methods for the analyses, missing data handling, and summaries of study data.

Patients will be followed during five years after randomization. Visits are programmed to occur 1 month, 3 months, 6 months and 12 months after randomization, where the primary end point will be accessed, however visits were extended each 6 months until 60 months (18, 24, 30, 36, 42, 48, 54, and 60) after randomization to evaluate long-term hypertension control and other clinical measures, as described in the study flow chart.

## **STUDY FLOW CHART**



## **1.1 ELIGIBILITY CRITERIA**

### **1.1.1 INCLUSION CRITERIA**

- Adults aged between 18 and 65 years.
- Patients with hypertension using at least 2 antihypertensive drugs at full doses or more than two in moderate doses.
- Grade 1 and 2 Obesity: Body Mass Index (BMI) between 30.0 kg/m<sup>2</sup> and 39.9 kg/m<sup>2</sup>.

### **1.1.2 EXCLUSION CRITERIA**

- Blood pressure levels  $\geq$  180/120 mmHg
- Cerebrovascular disease (stroke) in the past 6 months.
- Cardiac disease (myocardial infarction, angina, coronary revascularization, heart failure) that occurred or were diagnosed in the past 6 months.
- Underlying psychiatric diseases: schizophrenia, bipolar disorder, severe depression, and psychosis.
- Kidney disease: diabetic nephropathy or creatinine clearance  $<$  30 mL/min.
- Individuals with secondary hypertension, except due to sleep apnea.
- Advanced peripheral artery disease.
- Patients with atrophic gastritis.
- Type 1 diabetes mellitus; Latent autoimmune diabetes of adults; type 2 diabetes mellitus with HbA1c  $>$  7.0%.
- Alcoholism or use of illicit drugs.
- Current tobacco smoking habit.
- Previous abdominal surgery (except for MacBurney, Pfannenstiel, and video laparoscopic cholecystectomy).
- Severe hepatic disease.
- Pregnant women or women at childbearing age not using effective contraceptive methods.
- Neoplasm occurring in the past 5 years.
- Use of immunosuppressant drugs, chemotherapy or radiotherapy.
- Inability to understand and adhere to the treatment or postsurgical recommendations.

## **2. OBJECTIVES**

### **2.1 PRIMARY OBJECTIVE**

To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone in reducing at least 30% of the total antihypertensive drugs, maintaining a controlled blood pressure (<140x90 mmHg) at 12 months, in obese hypertensive patients.

### **2.2 SECONDARY OBJECTIVES**

To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone, in obese hypertensive patients, on the following end points at 12 months:

- Number of antihypertensive drugs.
- Systolic blood pressure.
- Diastolic blood pressure.
- Body weight and BMI.
- Waist circumference.
- Fasting glucose levels, HbA1c and insulin resistance
- LDL-cholesterol levels.
- HDL-cholesterol levels.
- Triglyceride levels.
- Uric acid levels.
- High-sensitivity C-reactive protein levels.
- Heart anatomy (interventricular septum diastolic thickness) as evaluated by echocardiogram examination.
- Estimated 10-year risk for cardiovascular disease (Framingham Risk Score).
- Adverse events.
- Systemic blood pressure measured by Ambulatory Blood Pressure Monitoring (ABPM).
- Central pressure, augmentation index, and pulse wave velocity measured by

SphygmoCor®.

- Sleep quality as assessed by polysomnography.

To assess the effect of Roux-en-Y gastric bypass compared to medical treatment on all primary and secondary end points between 24 and 60 months of follow-up.

### **3. OUTCOMES**

#### **3.1 PRIMARY OUTCOME**

Reduction of at least 30% of the total number of antihypertensive drugs, while maintaining controlled BP levels (SBP < 140 and DBP < 90 mmHg) at 12 months.

#### **3.2 SECONDARY OUTCOMES**

Reduction of at least 30% of the total number of antihypertensive drugs, while maintaining controlled BP levels (SBP < 140 and DBP < 90 mmHg) will be evaluated at 24, 36, 48 and 60 months and the following secondary outcomes will be assessed at 12, 24, 36, 48 and 60 months:

- Number of antihypertensive drugs.
- Systolic blood pressure (measured at office visits)
- Diastolic blood pressure (measured at office visits)
- Body weight and BMI.
- Waist circumference.
- Fasting glucose levels, HbA1c and insulin resistance
- LDL-cholesterol levels.
- HDL-cholesterol levels.
- Triglyceride levels.
- Uric acid levels.
- High-sensitivity C-reactive protein levels.
- Heart anatomy (interventricular septum diastolic thickness) as evaluated by echocardiogram examination.
- Estimated 10-year risk for cardiovascular disease (Framingham Risk Score).

- Adverse events.
- Systolic and diastolic blood pressure measured by ABPM.
- Central pressure, augmentation index, and pulse wave velocity measured by SphygmoCor®.
- Sleep quality as assessed by polysomnography.

#### **4. SAMPLE SIZE DETERMINATION**

The study was initially designed to enroll 60 patients. During the conduction of the trial, the Steering Committee decided to increase the sample size to 100 patients to improve precision of the effect estimate. This revised sample provides 90% power to detect an increase in the rate of the primary end point from 10% in the medical therapy to 40% in the gastric bypass group, assuming a two-sided hypothesis test with a significance level of 5%.

#### **5. STATISTICAL ANALYSIS**

##### **5.1 GENERAL CONSIDERATIONS**

Statistical analysis will be performed with the software R (R Foundation for Statistical Computing, Vienna, Austria)<sup>1</sup> in their latest version.

Baseline characteristics were reported as counts and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate.

The significance level will be 0.05 for all analysis. P values will not be adjusted for multiple comparisons.

##### **5.2 ANALYSIS POPULATIONS**

All the outcomes will be analyzed considering the Intention-to-treat population, that is, all subjects will be considered in the final analysis in the randomized assignment group, regardless of whether or not gastric bypass plus medical therapy or medical therapy only was used.

As sensitivity analyses we should compare the main results considering different populations definitions:

- Per-protocol: Considering all the subjects that actually adhere to the randomized



group. Subjects randomized to the medical therapy group who decide to have bariatric surgery **will not be included** in the per-protocol population. And subjects allocated to the gastric bypass group that don't undergo the surgery for any reason **will also not be included** in the per-protocol population.

- As-treated: Defined similarly to the per-protocol population. Subjects randomized to the medical therapy arm who decide to have bariatric surgery **will be included in the other arm** (if the procedure used was Roux-en-Y gastric bypass). Equally, subjects randomized to gastric bypass group that do not perform the surgery **will be followed and analyzed in medical therapy only group**.

### 5.3 MISSING DATA

Losses to follow up and consent withdraw may occur. In those cases, we intend to impute the missed **primary end point** using the last observation carried forward procedure<sup>2</sup> if the subject performed at least one of the follow up visits before the 12-month visit. Consequently, patients that were randomized and did not perform any follow up visit will not be considered in the primary hypothesis test. We will carry out complete case analysis for all other end points.

As a sensitivity analysis, we will use imputation of primary end point data assuming the worst-case scenario: missed value treated as positive end point for the control group and negative end point for the gastric bypass group.

### 5.4 ANALYTICAL METHODS

The effect on the primary end point will be expressed as rate ratio and 95% confidence interval, and assessed using Fisher exact test.

We intend to perform for the primary end point an adjusted analysis for BMI, number of medications at baseline, Framingham risk score, serum insulin level at baseline and duration of hypertension using Poisson regression analysis with robust error variance<sup>3</sup>.

Continuous secondary end points will be analyzed with adjustments for baseline values using repeated measures ANOVA models. Variables that do not hold normal distribution assumption will be analyzed using generalized estimating equation models with distribution that fit better the data. In those cases we will evaluate the model with several distributions

such as Gamma, Poisson, Inverse-Normal, and Beta, suggested according to the empirical distribution<sup>4</sup>.

Number of medications (secondary end point) will be tested at 12 month using Mann-Whitney test, medians difference will be presented as effect measure with 95% CI estimated by Bootstrap method with 1.000 replicates.

Adverse events will be compared among the groups according to the Fisher exact test at 12 month.

We plan to publish the trial results as soon we complete the 12-month follow-up for all patients, and publish the long-term analysis in a second paper. Consequently, to address the primary end point, and the number of medications, in the following visits we will adjust generalized estimating equation model with Poisson regression analysis with robust error variance<sup>3</sup> considering the time dependence in the following publications.

## **5.5 GRAPHS**

We will elaborate a graph showing the flow of patients through the stages of screening, enrolment, randomization, treatment and analysis.

We will also elaborate graphs showing: 1) the proportion of patients who meet the primary end point in both treatment groups; 2) The proportion of patients with controlled blood pressure (<140x90mmHg) and needing 0, 1, 2, or 3 or more antihypertensive medications, and the proportion of patient with uncontrolled blood pressure according to treatment groups; 3) Body mass index according to treatment group and time; 4) Systolic and diastolic blood pressure according to treatment group and time.

## 6. REFERENCES

1. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2017; URL <https://www.R-project.org/>.
2. Shao J, Zhong B. Last observation carry-forward and last observation analysis. *Stat Med* 2003; 22(15):2429–41.
3. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; 159:702-706
4. Hardin JW, Hilbe JM. Generalized estimating equations, 2<sup>nd</sup> ed. Chapman and Hall/CRC, Boca Raton, 2012. 277p.

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Page 1 version number and date updated			
Version 1.0 Date Jan/14/2013		Version 2.0 Date Dec/15/2016	
Page 3-4 Section 1 – additional sentence and study flow chart			
<p>This SAP contains the description of the sample size determination process, definitions of analysis populations, <del>outcomes</del>, details on the statistical methods for the analyses, and summaries of study data.</p> <p><del>Patients will be followed for 24 months after the randomization with visits schedule in 1, 3, 6, 12, 18 and 24 months.</del></p>		<p>This SAP contains the description of the sample size determination process, definitions of analysis populations, <b>end points</b>, and details on the statistical methods for the analyses, <b>missing data handling</b>, and summaries of study data.</p> <p>Patients will be followed during five years after randomization. Visits are programed to occur 1 month, 3 months, 6 months and 12 months after randomization, where the primary end point will be accessed, however visits were extended each 6 months until 60 months (18, 24, 30, 36, 42, 48, 54, and 60 months) after randomization to evaluate long-term hypertension control and other clinical measures, as described in the study flow chart.</p> <p>STUDY FLOW CHART INCLUSION</p>	
Page 5 Section 1.1 Inclusion Criteria			
<ul style="list-style-type: none"><li>Adults aged between18 to 65 year-old.</li><li>Patients with hypertension using at least 2 antihypertensive drugs at full doses</li><li>Class 1 and 2 obesity: Body Mass Index (BMI) between 30.0 and 39.9 Kg/m2.</li></ul>		<ul style="list-style-type: none"><li>Adults aged between 18 and 65 years.</li><li>Patients with hypertension using at least 2 antihypertensive drugs at full doses <b>or more than two in moderate doses.</b></li><li>Grade 1 and 2 Obesity: Body Mass Index (BMI) between 30.0 kg/m² and 39.9 kg/m².</li></ul>	
Page 5 Section 1.1 Exclusion Criteria			
<ul style="list-style-type: none"><li>Blood pressure levels ≥ 180/120 mmHg;</li><li>Cerebrovascular disease (stroke) in the past 6 months.</li></ul>		<ul style="list-style-type: none"><li>Blood pressure levels ≥ 180/120 mmHg;</li><li>Cerebrovascular disease (stroke) in the past 6 months.</li></ul>	

<ul style="list-style-type: none"> <li>• Cardiac disease (myocardial infarction, angina, heart failure) in the past 6 months.</li> <li>• Psychiatric diseases: schizophrenia, bipolar disorder, severe depression, psychosis.</li> <li>• Kidney disease: (diabetic nephropathy, creatinine clearance &lt; 30 ml/min).</li> <li>• Patients with secondary hypertension except due to sleep apnea.</li> <li>• Advanced peripheral arterial disease</li> <li>• Atrophic gastritis</li> <li>• Type 1 diabetes mellitus or Latent autoimmune diabetes of adults; Type 2 diabetes mellitus with HbA1c&gt;7.0%.</li> <li>• Alcoholism or illicit drug use</li> <li>• Current tobacco smoking habit</li> <li>• Previous laparotomy (except through MacBurney incision, Pfannenstiel incision and videolaparoscopic cholecystectomy)</li> <li>• Severe liver disease</li> <li>• Pregnancy or women not using effective birth control methods.</li> <li>• Neoplasia in the past 5 years.</li> <li>• Immunosuppressive drug treatment, chemotherapy or radiotherapy.</li> <li>• Inability to understand and adhere to treatment and post-surgical recommendations</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiac disease (myocardial infarction, angina, coronary revascularization, heart failure) that occurred or were diagnosed in the past 6 months.</li> <li>• Underlying psychiatric diseases: schizophrenia, bipolar disorder, severe depression, and psychosis.</li> <li>• Kidney disease: diabetic nephropathy or creatinine clearance &lt; 30 mL/min.</li> <li>• Individuals with secondary hypertension, except due to sleep apnea.</li> <li>• Advanced peripheral artery disease.</li> <li>• Patients with atrophic gastritis.</li> <li>• Type 1 diabetes mellitus; Latent autoimmune diabetes of adults; type 2 diabetes mellitus with HbA1c &gt; 7.0%.</li> <li>• Alcoholism or use of illicit drugs.</li> <li>• Current tobacco smoking habit.</li> <li>• Previous abdominal surgery (except for MacBurney, Pfannenstiel, and video laparoscopic cholecystectomy).</li> <li>• Severe hepatic disease.</li> <li>• Pregnant women or women at childbearing age not using effective contraceptive methods.</li> <li>• Neoplasm occurring in the past 5 years.</li> <li>• Use of immunosuppressant drugs, chemotherapy or radiotherapy.</li> <li>• Inability to understand and adhere to the treatment or postsurgical recommendations.</li> </ul>
<b>Page 6 Section 2.2 Secondary objective</b>	
<ul style="list-style-type: none"> <li>• To evaluate the effects of Roux-en-Y Gastric Bypass on systemic blood pressure assessed by ambulatory blood pressure monitoring (ABPM) at 12 and 24 months</li> </ul> <p>6. To evaluate the effects of Roux-en-Y Gastric Bypass on central blood pressure augmentation index and pulse wave</p>	<p>To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone, in obese hypertensive patients, on the following end points at 12 months:</p> <ul style="list-style-type: none"> <li>• Number of antihypertensive drugs</li> </ul>

velocity as measured by the SphygmoCor® device.

7. To evaluate the effects of Roux-en-Y Gastric Bypass on the systolic arterial blood pressure
8. To evaluate the effects of Roux-en-Y Gastric Bypass on the diastolic arterial blood pressure.
9. To evaluate the effects of Roux-en-Y Gastric Bypass on weight loss and BMI.
10. To evaluate the effects of Roux-en-Y Gastric Bypass on waist circumference.
11. To evaluate the effects of Roux-en-Y Gastric Bypass on glucose levels, HbA1c and insulin resistance.
12. To evaluate the effects of Roux-en-Y Gastric Bypass on LDL-cholesterol levels.
13. To evaluate the effects of Roux-en-Y Gastric Bypass on HDL-cholesterol levels.
14. To evaluate the effects of Roux-en-Y Gastric Bypass on triglycerides levels.
15. To evaluate the effects of Roux-en-Y Gastric Bypass on uric acid levels.
16. To evaluate the effects of Roux-en-Y Gastric Bypass on high-sensitivity C-reactive protein levels.
17. To evaluate the effects of Roux-en-Y Gastric Bypass on the reduction of risk of cardiovascular diseases (Framingham Risk Score).
18. To evaluate the effects of Roux-en-Y Gastric Bypass on heart anatomy.
19. To describe the main adverse events related to surgery

- Systolic blood pressure.
- Diastolic blood pressure.
- Body weight and BMI.
- Waist circumference.
- Fasting glucose levels, HbA1c and insulin resistance
- LDL-cholesterol levels.
- HDL-cholesterol levels.
- Triglyceride levels.
- Uric acid levels.
- High-sensitivity C-reactive protein levels.
- Heart anatomy (interventricular septum diastolic thickness) as evaluated by echocardiogram examination.
- Estimated 10-year risk for cardiovascular disease (Framingham Risk Score).
- Adverse events.
- Systemic blood pressure measured by ABPM
- Central pressure, augmentation index, and pulse wave velocity measured by SphygmoCor®.
- Sleep quality as assessed by polysomnography.

To assess the effect of Roux-en-Y gastric bypass

	compared to medical treatment on all primary and secondary end points between 24 and 60 months of follow-up.
<b>Page 7 Section 3.2 Secondary outcomes</b>	
<ul style="list-style-type: none"> <li>• 3.2 Secondary outcomes</li> <li>• Proportions of patients with a reduction of at least 30% in the total antihypertensive drugs at 6 and 24 months.</li> <li>• Change from baseline values on the following parameters, at 12 and 24 months, obtained by <ul style="list-style-type: none"> <li>○ Ambulatory Blood Pressure Monitoring (ABPM)</li> <li>○ Office blood pressure</li> <li>○ Central pressure measured by SphygmoCor® device</li> <li>○ Augmentation index measured by SphygmoCor® device</li> <li>○ Pulse wave velocity measured by SphygmoCor® device</li> </ul> </li> <li>• Change from baseline values on office systolic blood pressure</li> <li>• Change from baseline values on office diastolic blood pressure</li> <li>• Change from baseline values on weight and BMI, in-office measurements</li> <li>• Change from baseline values on fasting glucose levels, HbA1c, and insulin</li> <li>• Change from baseline values on LDL-cholesterol</li> <li>• Change from baseline values on HDL-cholesterol</li> <li>• Change from baseline values on triglycerides</li> <li>• Change from baseline values on uric acid</li> <li>• Change from baseline values on waist and hip circumference</li> <li>• Mean differences on the cardiac anatomy assessed by echocardiogram</li> <li>• Mean differences on the Framingham calculated risk</li> <li>• Description and incidence of any adverse events.</li> </ul>	<p>3.2 Secondary outcomes</p> <p>Reduction of at least 30% of the total number of antihypertensive drugs, while maintaining controlled BP levels (SBP &lt; 140 and DBP &lt; 90 mmHg) will be evaluated at 24, 36, 48 and 60 months and the following secondary outcomes will be assessed at 12, 24, 36, 48 and 60 months:</p> <ul style="list-style-type: none"> <li>• Number of antihypertensive drugs</li> <li>• Systolic blood pressure (measured at office visits)</li> <li>• Diastolic blood pressure (measured at office visits)</li> <li>• Body weight and BMI.</li> <li>• Waist circumference.</li> <li>• Fasting glucose levels, HbA1c and insulin resistance</li> <li>• LDL-cholesterol levels.</li> <li>• HDL-cholesterol levels.</li> <li>• Triglyceride levels.</li> <li>• Uric acid levels.</li> <li>• High-sensitivity C-reactive protein levels.</li> <li>• Echocardiographic parameters</li> <li>• Estimated 10-year risk for cardiovascular disease (Framingham Risk Score).</li> <li>• Adverse events.</li> <li>• Systolic and diastolic blood pressure measured by Ambulatory Blood Pressure Monitoring (ABPM).</li> <li>• Central pressure, augmentation index, and pulse wave velocity measured by SphygmoCor®.</li> <li>• Sleep quality as assessed by polysomnography.</li> </ul>

<b>Page 8 Section 4. SAMPLE SIZE DETERMINATION</b>	
A sample size of 60 patients (30 in the surgery group and 30 in the clinical treatment group) is necessary to detect a 40% difference in the incidence of the primary binary outcome (reduction of at least 30% of the drug prescription) between groups, assuming a bilateral hypothesis test with a significance level of 5% and 90% statistical power. This 40% absolute difference represents the difference between the assumed 50% proportion of outcome incidence in the surgery group and 10% incidence in the clinical treatment group, i.e., it is expected that at least 50% of the patients allocated for the surgery group have a reduction of at least 30% in the prescription of the antihypertensive drugs and that this proportion in the control group is 10%.	The study was initially designed to enroll 60 patients. During the conduction of the trial, the Steering Committee decided to increase the sample size to 100 patients to improve precision the effect estimate. This revised sample provides 90% power to detect an increase in the rate of the primary end point from 10% in the medical therapy to 40% in the gastric bypass group, assuming a two-sided hypothesis test with a significance level of 5%.
<b>Page 8 Section 5.1 General considerations</b>	
Statistical analysis will be performed using the SAS software, version 9.3.	Statistical analysis will be performed with the software R (R Foundation for Statistical Computing, Vienna, Austria) <sup>1</sup> in their latest version.
<b>Page 8 Section 5.2 Analysis populations</b>	
<p>All the outcomes will be analyzed according to considering the intention-to-treat principle, that is, all subjects will be considered in the final analysis in the randomized assignment group, regardless of whether or not gastric bypass plus medical therapy or medical therapy only was used.</p> <p>As sensitivity analyses we should compare the main results considering also a per-protocol population defined as the subjects that actually adhere to the randomized group. Subjects randomized to the medical therapy group who decide to have bariatric surgery will not be included in the per-protocol population. And subjects allocated to the gastric bypass group that don't undergo the surgery for any reason will also not be included in the per-protocol population.</p>	<p>All the <b>end points</b> will be analyzed considering...</p> <ul style="list-style-type: none"> <li>As-treated: Defined similarly to the per-protocol population. Subjects randomized to the medical therapy arm who decide to have bariatric surgery <b>will be included in the other arm</b> (if the procedure used was Roux-en-Y gastric bypass). Equally, subjects randomized to gastric bypass group that do not perform the surgery <b>will be followed and analyzed in medical therapy only group</b>.</li> </ul>



## Page 9 Added Section 5.3 Missing Data

Losses to follow up and consent withdraw may occur. In those cases, we intend to impute the missed **primary end point** using the last observation carried forward procedure<sup>1</sup> if the subject performed at least one of the follow up visits before the 12-month visit. Consequently, patients that were randomized and did not perform any follow up visit will not be considered in the primary hypothesis test. We will carry out complete case analysis for all other end points.

As a sensitivity analysis, we will use imputation of primary end point data assuming the worst-case scenario: missed value treated as positive end point for the control group and negative end point for the gastric bypass group.

## Page 9 Section 5.4 Analytical methods

The comparison of the proportions of those patients who present the primary outcome will be done using the Fisher exact test. Additionally, the relative risk with its respective 95% confidence intervals will be used as effect measures.

For the continuous variables, the differences between the average values alterations in relation to the baseline values, with their respective 95% confidence intervals will be calculated. Time dependence across variables will be modeled using repeated measures ANOVA models or Generalized Estimating Equations Models according to the data distribution.

The effect on the primary end point will be expressed as rate ratio and 95% confidence interval, and assessed using Fisher exact test.

We intend to perform for the primary end point an adjusted analysis for BMI, number of medications at baseline, Framingham risk score, serum insulin level at baseline and duration of hypertension using Poisson regression analysis with robust error variance<sup>3</sup>.

Continuous secondary end points will be analyzed with adjustments for baseline values using repeated measures ANOVA models. Variables that do not hold normal distribution assumption will be analyzed using generalized estimating equation models with distribution that fit better the data. In those cases we will evaluate the model with several distributions such as Gamma, Poisson, Inverse-Normal, and Beta, suggested according to the empirical distribution.

Number of medications (secondary end point) will be tested at 12 month using Mann-Whitney test, medians difference will be presented as effect measure with 95% CI

	<p>estimated by Bootstrap method with 1.000 replicates.</p> <p>Adverse events will be compared among the groups according to the Fisher exact test at 12 month.</p> <p>We plan to publish the trial results as soon we complete the 12-month follow-up for all patients, and publish the long-term analysis in a second paper. Consequently, to address the primary end point, and the number of medications, in the following visits we will adjust generalized estimating equation model with Poisson regression analysis with robust error variance<sup>3</sup> considering the time dependence in the following publications.</p>
<b>Page 10 Added Section 5.5 Graphs</b>	
	<p>We will elaborate a graph showing the flow of patients through the stages of screening, enrolment, randomization, treatment and analysis.</p> <p>We will also elaborate graphs showing: 1) the proportion of patients who meet the primary end point in both treatment groups; 2) The proportion of patients with controlled blood pressure (&lt;140x90mmHg) and needing 0, 1, 2, or 3 or more antihypertensive medications, and the proportion of patient with uncontrolled blood pressure according to treatment groups; 3) Body mass index according to treatment group and time; 4) Systolic and diastolic blood pressure according to treatment group and time.</p>